REMARKS

Paragraphs 0003, 0004, 0089 and 0098 of the specification have been amended to correct typographical errors.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made".

In the unlikely event that the transmittal letter is separated from this document and/or the Patent Office determines that an extension and/or other relief is required, Applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 50-1189**, referencing attorney billing no. 23888-7016. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

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By: Antoinette F. Konski

Antoinette F. Konski
Reg. No. 34,202

Bingham McCutchen LLP (formerly McCutchen, Doyle, Brown & Enersen LLP)
Three Embarcadero Center, Suite 1800
San Francisco, CA 94111-4067
Telephone: (650) 849-4950
Facsimile: (650) 849-4800

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

Paragraph 0003 at page 1 has been amended as follows:

Angiogenesis is the process through which new vascular structures arise by outgrowth from pre-existing capillaries, in this process, endothelial cells become detached from the basement membrane as proteolytic enzymes degrade this support. These cells then migrate out from the parent vessel, divide, and form into a newly differentiated vascular structure (Risau, (1997) Nature **386**:671-674; Wilting et al., (1995) Cell. Mol. Biol. Res. **41**(4):219-232). A variety of different biological factors have been found to function in controlling blood vessel formation (Bussolino et al., (1997) Trends in Biochem. Sci. **22**(7):251-256; Folkman and D'Amore, (1996) Cell **87**:1153-1155). These include proteins with diverse functions such as growth factors, cell surface receptors, proteases, protease inhibitors, and extracellular matrix proteins (Achen and Stacker, (1998) Int. J. Exp. Pathol. **79**:255-265; Devalaraja and Richmond, (1999) Trends in Pharmacol. Sci. 20(4):151-156; Hanahan, (1997) Science **277**:48-50; Maisonpierre et al., (1997) Science **277**:55-60; Suri [Sun] et al., (1996) Cell **87**:1171-1180; Sato et al., (1995) Nature **376**:70-74; Mignatti and Rifkin, (1996) Enzyme Protein **49**:117-137; Pintucci et al., (1996) Semin Thromb Hemost [l-Iemost] **22**(6)517-524; Vernon and Sage, (1995) Am. J. Pathol. **147**(4):873-883; Brooks et al., (1994) Science **264**:569-571; Koch et al., (1995) Nature **376**:517-519). The complexity of the angiogenic process and the diversity of the factors that control its progression provide a useful array of points for therapeutic intervention to control vascular formation *in vivo*.

Paragraph 0004 at page 2 has been amended as follows:

Angiogenesis normally occurs in a carefully controlled manner during embryonic development, during growth, and in special cases such as wound healing and the female reproductive cycle (Wilting and Christ, (1996) Naturwissenschaften **83**:153 -164; Goodger and Rogers, (1995) Microcirculation **2**:329-343; Augustin et al., (1995) Am. J. Pathol. **147**(2):339-351). Some of the important steps in the process of angiogenesis are: 1) growth factor (i.e. vascular endothelial growth factor, VEGF) signaling; 2) matrix metalloproteinases (MMP) and VEGF receptor interaction; 3) endothelial cell migration to site of growth factor signaling; 4) endothelial cell tubule formation. Pathological angiogenesis plays a central role in a number of human diseases including tumor growth and metastatic cancer, diabetic retinopathy, rheumatoid arthritis, and other inflammatory diseases such as psoriasis (Folkman, (1995) Nature Med. **I**(1):27-31; Polverini, (1995) Crit. Rev. Oral Biol. Med. **6(3)**:230-247; Walsh, (1999) Rheumatology **38**(2):103-112; Healy et al., (1998) Hum. Reprod. Update **4**(5):736-740[396]). In these cases, progression of disease is driven by persistent unregulated angiogenesis. For example, in rheumatoid arthritis, new capillary

blood vessels invade the joints and destroy the cartilage. In diabetic retinopathy, capillaries in the retina invade the vitreous, bleed and cause blindness. Significantly, tumor growth and metastasis are angiogenesis dependent. Most primary solid tumors go through a prolonged avascular state during which growth is limited to approximately 1-2 mm in diameter. Up to this size, tumor cells can obtain the necessary oxygen and nutrient supply by passive diffusion. These microscopic tumor masses can eventually switch on angiogenesis and recruit surrounding blood vessels to begin sprouting capillaries that vascularize the tumor mass, providing the potential for continuing expansion of the tumor and metastasis of malignant cells to distant location. Although significant progress has been made in understanding the biological events that occur during pathological angiogenesis, there are presently no effective pharmaceutical compounds that are useful for controlling angiogenesis *in vivo*. Thus, effective therapies capable of controlling angiogenesis have the potential to alleviate a significant number of human diseases.

Paragraph 0089 at page 21 has been amended as follows:

Example 2

Determination of Angiogenesis-Inhibition by Endothelial Cell Culture (ECC) Assay

The assays were carried out according to the procedures of Connolly[Connally], et al. (1986) Anal. Biochem. **152**:136-140[4] with modifications (Liang and Wong (1999) ANGIOGENESIS: FROM THE MOLECULAR TO INTEGRATIVE PHARMACOLOGY edited by Maradoudakis, Kluwer Academic/Plenum. Publishers, New York). D.T. Connolly et al. (1986) Anal. Biochem. **152**:136-140. CPAE (Cardiopulmonary Artery Endothelial Cells, bovine) acquired from American Type Tissue Culture (ATTC) were grown to nearly 95% confluence in MEM- 10E. The cells were released from the tissue culture flask with a 0.25% trypsin solution and plated in 24 well tissue culture plates in the same culture medium at a density of 10,000 cell/well. After the plates were cultivated for 8 hours at 37°C in a 5.0% $C0_2$ incubator. Assay samples and controls were added. Each sample was loaded in two different wells at 100 µL/well to insure reproducibility. After incubation with the sample for 60 hours, the medium was aspirated, and the number of cells was measured on the basis of the colorimetric measurement of cellular acid phosphatase.

Paragraph 0098 at page 24 has been amended as follows:

Example 9

MMP Assay

P.C. Brooks, et. al. (1996) in "Localization of matrix metalloproteinase MMP-2 to the surface of invasive cells by interaction with integrin αvβ3," (1996) Cell **85**:683-693 describes an *in vitro* assay on matrix metalloproteinase and αv/β3 integrin interaction. The effects of the experimental sample on the MMP-2/αvβ3 integrin complex determines if the sample's mechanism of action involves any disruption of this segment of the angiogenic pathway. This involves testing if the experimental sample can inhibit the interaction of MMP-2 with the αvβ3 integrin. Initially, this is done via an ELISA using antibodies for MMP-2 and testing the binding of these antibodies to the sample. Further studies are pursued if a positive result occurs. TIMP-2 (Tissue Inhibitor of Matrix Metalloprotease-2), a known natural inhibitor of MMP-2, is used as the control.